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Severe Ethylene Glycol Intoxication With Multisystem Failure

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SINCE ETHYLENE GLYCOL was originally synthesized at the turn of the century, many uses have been found for it, most notably as a primary component in commercial antifreeze.

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ABBREVIATIONS USED IN TEXT

CSF = cerebrospinal fluid
CT = computed tomographic

Formerly felt to be a nontoxic compound and even used as a carrier for early medicinals, it has since been shown to be a potentially lethal agent.[1] Ingestion of a significant quantity (greater than 75 to 100 ml) has resulted in a variety of biochemical derangements and multisystem failure, the most impressive of which are a refractory anion gap metabolic acidosis, oliguric or anuric acute renal failure and central nervous system dysfunction ranging from mild intoxication to coma and death.[1,2] Traditional treatment has centered on ethanol infusions of 5 to 15 grams per hour, to maintain ethanol blood concentrations of 1,000 μg per ml, and hemodialysis.[3,4,5]

We recently treated a patient who had a massive overdose of ethylene glycol that had gone unrecognized for 12 hours. In addition to the expected acidosis, coma and renal failure, cerebral edema and bone marrow arrest developed. The patient was treated with ethanol infusion and hemodialysis. Despite a seven-day period of coma, eight days of anuric renal failure and two weeks of pancytopenia, the patient survived.

Report of a Case

The patient, a 36-year-old man with a history of schizophrenia and idiopathic seizures treated with phenytoin, presented to a community hospital with ataxia and nystagmus that were initially diagnosed as a phenytoin overdose. His neurologic state deteriorated to stage 4 coma six hours after admission. At that time he was found to have a severe anion gap metabolic acidosis, which was treated with sodium bicarbonate. Toxicology screen was positive for ethylene glycol and negative for ethanol. Twelve hours after admission, an ethanol infusion was begun, and the patient was transferred to University of Colorado Health Sciences Center for further management.

On examination on arrival, he was comatose with Kussmaul's respirations. His blood pressure was 168/100 mm of mercury, pulse 122 and temperature 37.5°C (99.5°F) rectally. Bilateral papilledema without hemorrhages was noted. The neck was supple, and results of chest and cardiac examinations were normal. On neurologic examination he had spontaneous respirations but no response to deep pain, and a flaccid quadriparesis was present.

Blood gas determination on admission while the patient was breathing room air showed a pH of 7.00, a partial carbon dioxide pressure of 9 torr, a partial oxygen pressure of 108 torr and a base excess of −27 mEq per liter. The following laboratory values were elicited: serum sodium 157, potassium 3.4, chloride 100 and bicarbonate 4 mEq per liter; urea nitrogen 24 and creatinine 3.3 mg per dl, and the anion gap 53 mEq per liter. Hematocrit was 49% and the leukocyte count was 35,000 per μl. Analysis of urine showed numerous erythrocytes without casts and large numbers of needle-shaped crystals. Ethanol and ethylene glycol levels were 540 μg per ml and 4,650 μg per ml, respectively.

The patient was admitted to the intensive care unit and treated with sodium bicarbonate and a bolus of 30 grams of ethanol, followed by an infusion of 10 grams per hour of ethanol given as a 10% weight-per-volume infusion in 5%

dextrose and water. Hemodialysis was immediately instituted using a Century 1 machine with flow rates of 140 ml per minute through femoral venous catheters. The dialysate flow rate was 500 ml per minute. One hour after starting dialysis, inflow and outflow levels of ethanol were found to be 1,204 μg per ml and 344 μg per ml, respectively, indicating a dialysis clearance of 71% of the blood flow through the machine, or 6.0 liters per hour. This clearance removed 7.2 grams of ethanol per hour of dialysis. The ethanol infusion was increased to 17 grams per hour during dialysis to replace the hemodialysis losses. This dose maintained plasma ethanol levels at 1,200 μg per ml. Ethylene glycol clearance was calculated from the blood flow of 140 ml per minute, an inflow level of 1,794 μg per ml and an outflow concentration of 765 μg per ml, or 4.8 liters per hour. Dialysis was continued for 15 hours on day 1 and 8 hours on day 2 (at flow rates of 220 ml per minute, leading to an ethylene glycol clearance of 7.6 liters per hour) with rapid reduction in blood ethylene glycol levels and gradual control of acidosis (Figure 1).

The hospital course was complicated by prolonged coma with seizures, anuric renal failure and bone marrow arrest. After hemodialysis had removed all ethylene glycol, the patient remained comatose and had occasional grand mal seizures that were treated with phenytoin. To evaluate a persistent coma, a lumbar puncture was done on day 3. It showed an opening pressure greater than 450 mm of cerebrospinal fluid (CSF), protein 204 mg per dl, glucose 116 mg per dl and a cell count of 314 erythrocytes per μl and 13 leukocytes per μl, with 60% neutrophils, 11% lymphocytes and 29% mononuclear cells. Cultures were negative. A cranial computed tomographic (CT) scan showed central edema with relative sparing of the corona radiata and cortical gray matter

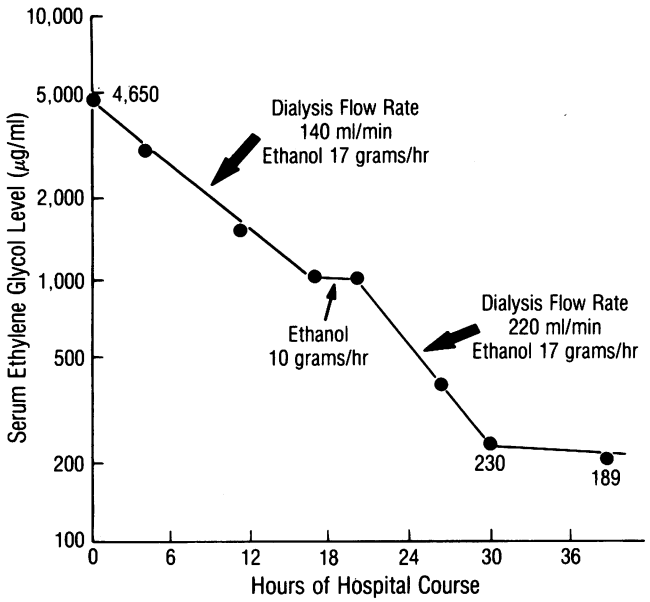

Figure 1.—Clearance of ethylene glycol by hemodialysis. From these data, ethylene glycol clearance was 4.8 liters per hour during the first dialysis period and 7.6 liters per hour when dialysis flow rate was increased from 140 to 220 ml per minute. In both instances, dialysis efficiency was 58%. Ethylene glycol half-life was 7.7 and 4.7 hours during the two intervals. Note that the ethylene glycol level does not fall in the time between dialyses. The ethanol clearance was 6 liters per hour during the first dialysis period, indicating an extraction efficiency of 71%.

but with compression of the lateral and third ventricles (Figure 2, Top). Dexamethasone, 6 mg intravenously every six hours, was administered for ten days. The patient remained comatose until day 7, when he responded to simple commands. Improvement thereafter was rapid, with ataxia and nystagmus resolving on day 10. Results of a neurologic examination on day 17 were normal, and a repeat cranial CT scan showed only mild central atrophy (Figure 2, Bottom).

The hemogram on admission was remarkable only for an impressive leukocytosis. The hematocrit fell rapidly, however, without evidence of hemolysis or blood loss. By day 3, the hematocrit was 27.3%, the leukocyte count 2,300 per μl with a normal differential, the platelet count 54,000 per μl and the uncorrected reticulocyte count 1.2%. A bone marrow biopsy specimen on day 4 showed granulocyte and megakaryocyte maturation arrest and total absence of erythroid precursors. Because a reversible red cell aplasia has been associated with phenytoin therapy, this drug was discontinued despite the fact that levels were never elevated. Packed red blood cells were given. Without other specific therapy, the hematocrit gradually returned to a level of 40% two months later. Following recovery of the hematocrit, the patient was restarted on a regimen of phenytoin and phenobarbital without ill effect.

Anuria persisted until day 8 and the patient required hemodialysis until day 12, when adequate renal function returned. By day 20, the creatinine value was 1.2 mg per dl and the urine analysis normal. Two months following discharge, the patient was seen in clinic and had normal renal and neurologic function. His schizophrenia persisted.

Discussion

Our patient presented the classical findings of massive ethylene glycol intoxication, including oxalic aciduria and acute renal failure. In addition, he suffered from prolonged coma and bone marrow arrest. These life-threatening complications have not been reported in the past and may have been the result of the 12-hour delay between ingestion and ethanol treatment. Complicating the clinical diagnosis was the fact that the patient did not have classical envelope-shaped crystals of calcium oxalate dihydrate in his urine. However, needle-shaped crystals of calcium oxalate monohydrate may be seen in patients with ethylene glycol overdose.[6,7] Nonketotic anion gap acidosis should always alert a physician to the possibility of a drug overdose of ethylene glycol, methanol or salicylates.

Central nervous system pathology is a frequent component of the overall presentation in cases of ethylene glycol intoxication. A meningoencephalitis with elevated CSF pressure, increased protein and CSF pleocytosis is not uncommon.[1,3] Papilledema is seen and is usually due to cerebral edema, but occasionally it represents a toxic optic neuropathy with progressive loss of vision and optic atrophy, similar to that seen in methanol ingestion.[8] The central edema in our case is unique, however. The peculiar distribution of edema in our patient was not in a specific vascular territory, nor isolated to areas predisposed to damage by other noxious insults. Despite this severe pathology, the patient recovered without neurologic sequelae.

A second life-threatening complication in this patient was bone marrow arrest. While the patient did receive phenytoin for seizures, he had taken this drug on a long-term basis

without ill effect and at no time had elevated plasma concentrations of this drug. No other known marrow toxic drugs were given. Neither ethylene glycol nor methanol has been associated with pancytopenia in the past but, by inference, we feel the acidic products of ethylene glycol may have led to the failure of the bone marrow in this patient. Furthermore, phenytoin therapy was restarted and has been maintained without recurrence of anemia.

Renal failure persisted for eight days but full recovery took place by day 20. Others have reported partial recovery of renal function even after 60 days of renal failure.[2]

Treatment of ethylene glycol poisoning has included ethanol infusion and hemodialysis. The rationale for using ethanol is that ethylene glycol is metabolized in the liver to the toxic metabolites glycolic, glyoxylic and oxalic acids. Ethanol can block the hepatic metabolism of ethylene glycol because ethanol has a much higher affinity for the enzyme alcohol dehydrogenase than does ethylene glycol. Because the unmetabolized ethylene glycol must be removed from the body by some route, and because it is not concentrated in the urine, the most efficient way to remove the compound is by hemodialysis.

Most physicians, including ourselves, administer ethanol to produce an ethanol level of 1,000 μg per ml to block the metabolism of ethylene glycol by alcohol dehydrogenase.[3,8,9] While this is a safe and effective practice, much lower concentrations can offer substantial protection. Ethanol is a 100-fold better substrate for alcohol dehydrogenase than is ethylene glycol.[10] In our patient, the initial ethylene glycol level was 4,650 μg per ml. Ethanol, at a concentration of 1,000 to 2,000 μg per ml, will inhibit greater than 95% of the metabolism of ethylene glycol. But even at an ethanol concentration of 100 μg per ml, ethanol will still block 75% of ethylene glycol metabolism. Clearly, the higher the ethanol, the greater the blockade, but even small amounts of ethanol can be valuable in preventing ethylene glycol toxicity.

For successful treatment, both a loading and a maintenance dose of ethanol must be given. The volume of distribution of ethanol is that of body water, or approximately 60% of body weight. Thus, in a 70-kg (154-lb) man with a 42-liter volume of distribution, an initial bolus of 42 grams absolute ethanol will yield a blood alcohol concentration of 1,000 μg per ml (this amount of ethanol is present in about 4 oz of 80-proof whiskey). Average hepatic metabolism will require

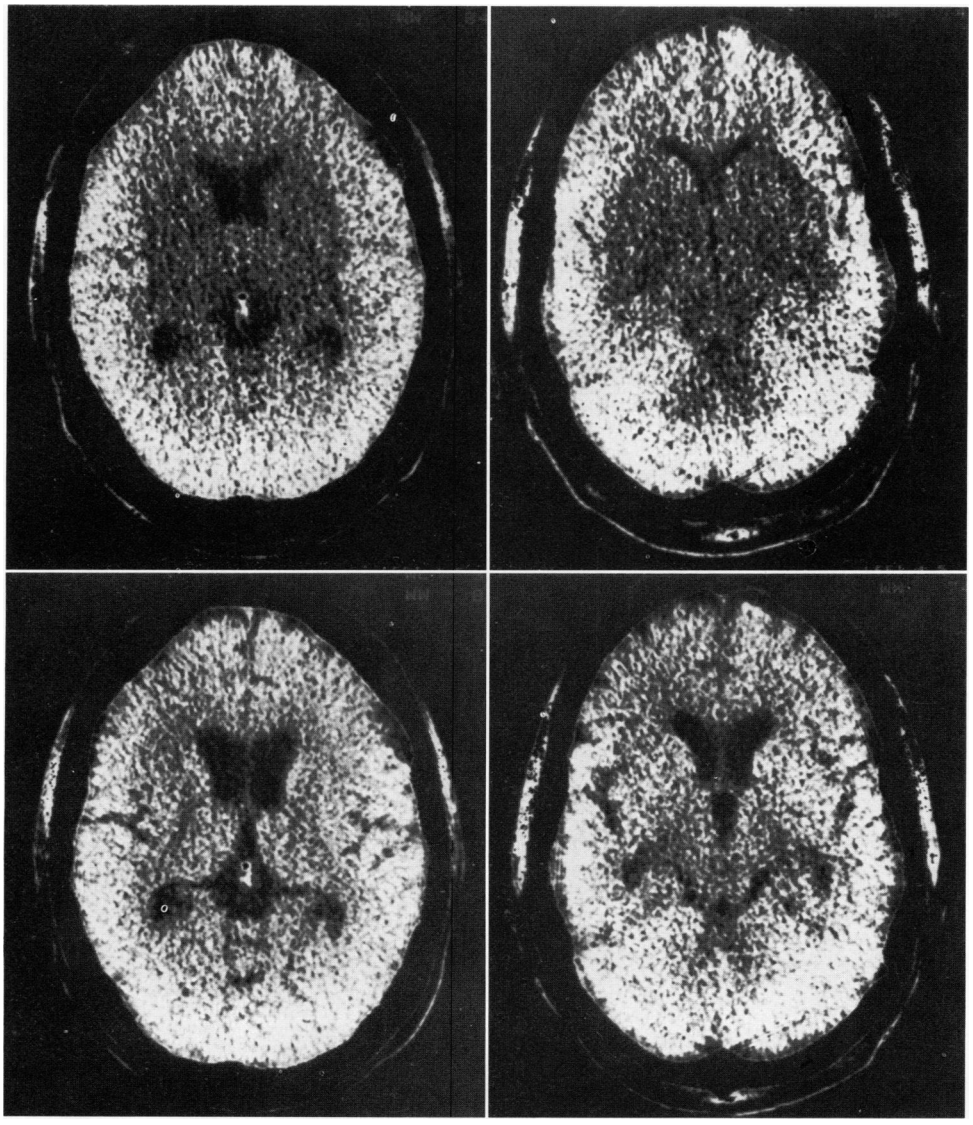

Figure 2.—Top, Computed tomographic (CT) scans show cerebral edema on day 3 following ethylene glycol overdose. **Bottom,** CT scans were taken on day 17 when patient had normal neurologic findings. Cerebral edema has resolved.

a constant infusion of 8 to 10 grams per hour to maintain that level, but only frequent blood level determinations can prevent underdosing or overdosing a patient. When hemodialysis is started, additional ethanol must be given to replace that cleared by the dialysis machine. As noted in this case, 7 grams per hour was cleared by dialysis so that a total of 17 grams per hour ethanol had to be given to allow for both hepatic and dialysis removal. An alternative to measuring clearance across the dialysis machine is to supply a concentration of ethanol of 1,000 μg per ml to the dialysis bath. In our machine, dialysate flowed at a rate of 500 ml per minute. This flow rate would require 30 grams ethanol per hour to be added to the dialysate.

An unresolved question in toxic alcohol overdoses is what constitutes a "safe" level of toxin. Our patient survived despite a prolonged period of profound acidosis, cerebral edema and anuric renal failure. Because acidosis alone would not be expected to produce these complications, the glycol aldehyde and glycolic, glyoxylic and oxalic acids must have intrinsic toxicities. Assuming that the maximum rate of metabolism of ethylene glycol is similar to that of ethanol, about 200 mEq per hour of acid will be generated at very high ethylene glycol concentrations (2,000 to 5,000 μg per ml). This enormous acid load rapidly overwhelms the buffering capacity of the body. With an ethylene glycol level below 500 μg per ml, acid production will be only about 20 mEq per hour. Patients with normal renal function can probably compensate for this rate of acid generation and so these patients will probably not require treatment. In cases of renal failure, calcium oxalate crystals are present in the tubules.[2] We would agree with traditional guidelines that have suggested that crystalluria and metabolic acidosis are the indications for therapy.[3,11]

It has recently been suggested that ethanol be administered orally rather than intravenously.[11] While early loading with any source of oral ethanol in a conscious patient is desirable, there is no reason to believe oral ethanol dosing is superior to intravenous. Ethanol in the bloodstream may inhibit its own intestinal absorption, even at levels considered by most to be therapeutic.[12] The absorption of ethanol is also dependent on other substances present in the stomach and duodenum. Lipids, for example, cause delayed gastric emptying and hence delayed absorption. Intrinsic bowel motility is also a factor. In many seriously ill patients, an adynamic ileus is present, resulting in unpredictable effects on ethanol uptake from the gut.

The critical importance of hemodialysis in the treatment of ethylene glycol poisoning must be emphasized. While an ethanol infusion can prevent most metabolism of ethylene glycol, the toxic alcohol, aldehyde metabolites and organic acids must be removed. Diuresis is impractical because alcohols cannot be concentrated in the urine,[13] and 40 to 80 liters of urine output would be required to remove most of the ethylene glycol present. In addition, severe poisonings are frequently complicated by acute oliguric or anuric renal failure. Hemodialysis, by contrast, can clear at rates of at least 60% of the blood flow rate through the coil. For this reason, all patients with ethylene glycol ingestion should be loaded with ethanol and transferred to a hemodialysis facility.

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